REMARKS

Claims 1-3, 8-10, 18-20, and 27-30 are pending.

Claims 1-3, 8-10, 18-20, and 27-30 were all previously allowed (Office Action of 15 July 2004, and Office Communication dated 24 February 2005), however, except for claims 27 and 28, which remain allowed, Claims 1-3, 8-10, 18-20, and 28-30 were rejected when a new Examiner took over the case when the prior Examiner left on maternity leave.

Applicants thank the Examiner for withdrawing the improper Notice of Abandonment mailed May 2, 2007, and the Advisory Action mailed April 17, 2007.

Applicants acknowledge the Examiner's maintained rejection of claims 1-3, 8-10, 18-20, and 29-30, under 35 USC 112 first paragraph as allegedly lacking *enablement*. Applicants have respectfully *traversed* this rejection.

Applicants acknowledge the Examiner's *new grounds* of rejection of claims 8-10, 18, 29, and 30, under 35 USC 112 first paragraph as allegedly lacking *written description*. Applicants have respectfully *traversed* this rejection.

No new matter has been added.

FORMALITIES

Inconsistent Protracted Examination. Applicants respectfully maintain the objection to the present inconsistent, protracted, expensive, burdensome examination, and the non-responsiveness by the Office. Applicants' statements in this regard are of record in this case and are hereby reaffirmed and reasserted. Applicants reiterate that Applicants' various applications covering this subject matter are additionally now split between two different art groups with different Supervisory Examiners, and again respectfully request that the subject matter be consolidated in a

single art group with the original Examiner Anne L. Holleran who is responsible for Applicants' other related cases on this subject matter, so that a more efficient and consistent Examination can be conducted and finalized.

35 U.S.C. §112, first paragraph

Claims 1-3, 8-10, 18-20, and 29-30 stand rejected, under 35 U.S.C. §112, first paragraph, allegedly for reasons previously set forth in the paper mailed July 26, 2006, section 4, pages 2-9. As an initial matter, Applicants note that the original rejection cited in the paper mailed July 26, 2006, included only claims 1-2, 8-9, 18-20, and 29-30. Applicants respectfully note that no new reason has been made of record as to why claims 3 and 10 are now included in this rejection.

Specifically, the Examiner alleges that the scope of the claims is not commensurate with the teachings of the specification. It is conceded that the specification is enabling for an isolated polypeptide *consisting of* SEQ ID NO:1 or comprising SEQ ID NO:2. However, the Examiner urges that the specification allegedly does not reasonably provide enablement for any polypeptide comprising SEQ ID NO:1, having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419 or about 350-419 amino acids from SEQ ID NO:2, which bind to the extracellular domain of HER-2.

The Examiner contends that the rejections have been maintained as Applicants' previous arguments of record allegedly provided no nexus between the appropriate caselaw and the instant pending claims. Applicants respectfully disagree with the Examiner's mischaracterization of Applicants' previous arguments of record. However, solely to expedite prosecution, and without acquiescing to this basis of rejection, Applicants respectfully submit that the pending claims are fully enabled by the instant application as filed.

Relevant Law:

Applicants maintain that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir., 1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. In Atlas, Du Pont sold a gelled slurry blasting agent until the latter part of the 1970's. In 1976, Du Pont formed a team to study the feasibility of an emulsion blasting agent. The team succeeded in making a water-in-oil emulsion blasting agent which Du Pont began making and selling in August 1978. Atlas sued for patent infringement in December 1979.

In the cited case, Du Pont claimed Atlas' allegedly infringed patent was invalid due to lack of enablement and alleged that the patent disclosure lists numerous salts, fuels, and emulsifiers that could form thousands of emulsions but that there was no commensurate teaching as to which combination would work. The disclosure, according to Du Pont, was nothing more than "a list of candidate ingredients" from which one skilled in the art would have to select and experiment unduly to find an operable emulsion. The district court held it would have been impossible for the inventor to list all operable emulsions and exclude the inoperable ones. Further, it found such list unnecessary, because one skilled in the art would know how to select a salt and fuel and then determine the proper emulsifier using basic principles of chemistry. The Federal Circuit agreed, and held that Atlas' claims did not lack enablement.

Similarly, as in the instant pending claims, while the genus may encompass multiple polypeptides that may require some routine screening to determine which specific polypeptides fall within the scope of the instant claims, such procedures are not only taught in the instant

specification in detail, but are also standard in the art and amount to no more than routine experimentation (not undue experimentation). As in Atlas, basic principles of the art (there in determining operable emulsions in the claimed genus and here in determining operable polypeptides in the claimed genus) are well within the general purview of the skilled artisan, in view of the instant teachings and knowledge in the art at the time of filing of the present specification.

This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 471 F.2d 1237, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. In In re Anderson, all of appellant's claims in an application for a patent for a surgical dressing were rejected by the patent examiner, and the rejection was affirmed by the Patent Office Board of Appeals. The claims were rejected on the grounds that they were broader than warranted by the disclosure, were indefinite, and improperly introduced new matter. The appellate court held: 1) appellant was entitled to broad claims that defined his invention without a reference to specific instrumentalities; 2) appellant's claim did not need to exclude all other materials, when it referred to "medicament" in order to be valid, but merely to point out what the combination was; 3) appellant's claim as to one of the compositions of one of the dressing layers was indefinite; and 4) amendment to claim did not introduce new matter which warranted rejection.

In allowing broad claims for "medicaments," the court stated that, "There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. In re Anderson, at 1241 (citing Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

On the issue of enablement, the court described the layered dressings as combination claims, and stated that appellant need not include elements in the claims that restrict the claimed subject matter in that the claims encompass medicaments that are not operative for appellant's stated

purpose. Instead, the court held that the genus of claimed medicaments were adequately identified by exemplary embodiments in the specification, such that, "there is no practical way to restrict the claim language so as to exclude all inoperative or deleterious medicaments," which would result in obscure claims. Id. at 1243.

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). There is, therefore, no requirement for disclosure of every species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed.

In In re Grimme, Keil, and Schmitz, the patent applicant appealed from the decision of the Board of Appeals of the United States Patent Office affirming the rejection by the Primary Examiner of the single claim of appellants' application for a patent on penicillin salts of amino salicylates.

With regard to the claim scope, the court stated that the instant application and previous parent application fully supported the genus claims. In doing so, the court stated that, "It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." Id. at 789.

Applicants respectfully submit that the Examiner has not established a *prima facie* case of lack of enablement, as the proper inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require ***undue*** experimentation to make and use the

subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Wands Analysis:

Applicants reaffirm and reassert Applicants' previous arguments of record. As described below, a consideration of the factors enumerated in In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art as well as the other relevant factors, teaches how to make and use the full scope of the claimed subject matter.

Applicants submit that general techniques for isolating, expressing, and testing polypeptides comprising all or part of the sequence of p68HER-2 set forth in SEQ ID NO:2, including the ECDIIIa portion set forth in SEQ ID NO:1, are provided in the specification and are known to the skilled artisan, as discussed in detail below. Any necessary adjustment or alteration to the claimed sequences can be readily determined using mere routine testing. Applicants teach the full length polypeptide and the ECDIIIa portion, and demonstrate binding thereof in the instant application as filed. Applicants further teach screening assays for testing polypeptides or fragments thereof in order to assess activity of the polypeptides or fragments thereof. Applicants explicitly teach and disclose a requirement for at least 50-79 contiguous ECDIIIa amino acid residues in the inventive polypeptides. *See* lines 3-13, page 3, and also Affidavits by Dr. Gail Clinton, submitted January 26, 2007.

Applicants reiterate that the Wands analysis fully supports Applicants' position that the instant specification fully enables the scope of the pending claims. The Wands factors are set forth below:

1) Scope of the Claims. The claims are directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}, as well as pharmaceutical compositions thereof. Dependent claim 2 specifies that the polypeptide of claim 1 is from about 69 to 79 amino acids in length. Claim 8 is directed to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, or fragments thereof that are about 80 to 419 amino acids in length that contain the 79 amino acid C-terminal portions and that bind to the ECD of HER-2. Dependent claim 9 specifies that the polypeptide is from about 350 to 419 amino acids in length and contains three N-linked glycosylation sites. Claims 18-20 and 29-30 are directed to pharmaceutical compositions containing the polypeptides set forth in claims 1-2 and 8-9, respectively.

The claims are clearly within the scope of what is taught in the specification, *i.e.*, a genus of polypeptides of p68HER-2 that includes the particular claimed polypeptides. The specification teaches that p68HER-2 binds to the ECD of HER-2, teaches that a fragment thereof having 79 amino acids also binds to the ECD of HER-2, and further teaches that fragments thereof having 50-79 amino acids also bind to the ECD of HER-2. The specification teaches the sequence, expression, cloning, and purification of p68HER-2 and related truncated polypeptides (*i.e.* the 79 amino acid ECDIIIa peptide), and provides detailed assays for assessing their binding affinity. Applicants respectfully submit that such screening assays are merely routine in the art, do not amount to undue experimentation, and are not solely relied upon given that the specification explicitly teaches the

specific sequences of the fragments and subfragments claimed. Applicants submit that by following the teachings of the specification, one of skill in the art can readily make the claimed polypeptides and measure the binding affinity of the polypeptides. Therefore, the scope of the claims is commensurate with the teachings of the specification.

2) Level of Skill in the Art. The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled artisan and provide further evidence of the high level of skill in this art.

3) Knowledge of those of Skill in the Art. At the time of filing of the instant application, a broad body of knowledge was available and known about HER-2 and other tyrosine kinases. Many of these articles and patents have been made of record in this application. For example, the sequence of HER-2 was known, its structural and biochemical properties had been determined, and its overexpression was associated with a variety of carcinomas. Truncated variants containing regions of the extracellular domain (ECD) of a variety of HER receptor tyrosine kinase family members were also known, many of them produced by proteolytic processing of full length receptors or by alternative processing (see *e.g.*, Lee and Maihle, (1998) Oncogene, 16:3243).

In one example, truncated variants of HER-2 were known and analyzed for function. Among these include a proteolytically shed product containing the extracellular domain (ECD) found in breast carcinomas, and a truncated ECD of HER-2 generated as an alternative transcript (see *e.g.*, Scott et al., (1993) Mol. Cell. Biol. 13:2247). In addition, a truncated ECD of related EGFR also was known, and was characterized as exhibiting ligand-binding, and affecting the function of receptor activation and signaling (see *e.g.*, Basu *et al.*, (1989) *Mol. Cell. Biol.*, 9:671).

The above references exemplify a variety of published protocols for the identification, production and/or analysis of truncated receptor tyrosine kinase products, including truncated HER-

2 polypeptides, and the analysis of such peptides in binding assays and/or or other functional assays. These references provide an independent source of evidence that verifies such procedures were part of the routine experimentation for the skilled artisan at the time of filing of the application. Thus, these references represent the state of the art at the relevant time.

4) Teachings of the Specification and Working Examples. As discussed herein, the claims are directed to p68HER-2 polypeptides and fragments thereof that bind to the ECD of HER-2 with a binding affinity of $10^8 M^{-1}$. Included among these polypeptides are polypeptides or fragments of polypeptides having the sequence of amino acids set forth in SEQ ID NO:1 or SEQ ID NO:2. Hence, the "genus" encompasses the exemplified species and other species that are similar to the exemplified species because they exhibit all or part of the sequence of SEQ ID NO:1 or SEQ ID NO:2 and have binding affinity for the ECD of HER-2. The specification teaches such genus of polypeptides and teaches their sequence, cloning, expression, and purification and assays to test their binding affinity to the ECD of HER-2.

The specification teaches the detailed structural and functional characterization of a naturally occurring inhibitor of HER-2, p68HER-2. The specification describes that p68HER-2 binds to p185HER-2 and that the binding affinity of p68HER-2 resides in the novel proline rich ECDIIIa domain, rather than the N-terminal subdomains I and II of p68HER-2. The specification teaches that the proline rich ECDIIIa domain is a retained intron 8 sequence of 79 amino acids. The specification teaches how to clone, purify, and test the binding affinity of the 79 amino acid fragment of p68HER-2. The specification teaches polypeptides comprising 50-79 contiguous residues of the 79 amino acid fragment of p68HER-2, and use thereof as presently claimed.

For reasons previously made of record, the Working Examples exemplify the teachings of the specification relating to the characterization, cloning, purification, and function of p68HER-2, and polypeptide fragments thereof (*i.e.* 79 amino acid fragment).

5) ***Predictability.*** While the unpredictability in the generally art of protein chemistry was high at the time that the instant application was filed, such unpredictability was mitigated by the high level of knowledge and skill in the art of identification, characterization, cloning, purification, and testing the claimed polypeptides, and a broad body of knowledge was available and known about HER-2 and other tyrosine kinases as described above under "*Knowledge of those of Skill in the Art*."

Thus, taking all of the Wands factors into account, Applicants respectfully submit that the skilled artisan could readily make and use the claimed subject matter given the instant application, and in light of the knowledge in the art at the time the application was filed.

Furthermore the specification teaches the entire sequence of the ECDIIIa domain polypeptides, demonstrates activity of several and provides assays to assess the activity of any others, including fusion proteins. Systematically removing residues and, if necessary, testing the resulting polypeptides for activity is routine and readily achieved. The full-length or truncated ECDIIIa region sequence of every such polypeptide is known in view of the disclosure of the application.

Applicants have submitted various Affidavits by inventor Dr. Gail Clinton (Already of record), which confirm, *inter alia*, that Applicants' explicit conception and disclosure had a reasonable scientific basis, and that Applicants were in possession of which amino acid residues of ECDIIIa are critical to binding to HER-2 receptor, and taught the same in the instant specification by recitation of the requirement for at least 50-79 contiguous amino acids of ECDIIIa in the claimed polypeptides. Also confirmed in said Affidavits, are binding studies of subsequently generated ECDIIIa non-conservative amino acid substitutions further confirm Applicants' conception and disclosure of the requirement for at least 50-79 contiguous amino acids of ECDIIIa in the claimed polypeptides.

Applicants respectfully submit that the claimed subject matter was enabled at the time of filing of the instant application since the claimed sequence and operative fragments thereof were disclosed in the application in such a manner that the skilled artisan could make and use the claimed subject matter. Applicants respectfully submit that the skilled artisan, provided with the sequences taught in the specification, and in light of the level of skill at the time that the application was filed, could readily identify and appreciate that the ECDIIIa polypeptide contained a stretch of contiguous hydrophobic amino acid residues centered in the ECDIIa region. Applicants respectfully further submit that the skilled artisan would readily appreciate that hydrophobic amino acid residues play an important role in folding, binding, and other protein-protein interactions of polypeptides.

Applicants respectfully submit that the claimed subject matter can be fully practiced without 'undue' experimentation, due to the guidance provided by the specification, including the explicit recitation of the requirement for at least 50-79 contiguous amino acids of ECDIIIa in the claimed polypeptides. Thus, the teachings of the specification fully enable the skilled artisan to make and use fragments of SEQ ID NO:1 or SEQ ID NO:2 that exhibit binding affinity to p185HER-2.

Applicants respectfully submit that the Affidavits by Dr. Gail Clinton (Already of record) not only further confirm that the specification is enabling, but additionally describe the reasonable scientific basis underlying Applicants' recitation of the requirement for at least 50-79 contiguous amino acids of ECDIIIa in the claimed polypeptides; that is, based on the hydrophobicity analysis set forth therein. Applicants note that the Federal Circuit has recently ruled that evidence submitted by applicants in rebuttal to a rejection, such as submitted declarations, must be given "meaningful consideration." In re Sullivan, p. 12, No. 08.405,454 (Fed. Cir., Aug. 29, 2007).

Specifically in In re Sullivan, the Federal Circuit vacated and remanded the decision of the Appeals' Board for failing to properly consider the declarations submitted as evidence in rebuttal to the rejection. The court stated that, "when an applicant puts forth relevant rebuttal evidence, as it

did here, the Board must consider such evidence." Id. The court went on to say that the rejection cannot be maintained if competent evidence rebuts the rejection, and that "[b]y failing to consider the submitted evidence, the Board thus committed error." Applicants submit that the previously submitted affidavits have not been given proper and "meaningful consideration," as rebuttal evidence to the rejection at hand, in light of the statement made therein relating to enablement of the claimed invention at the time that the application was filed. The Examiner's statement that the hydrophobicity analysis, obtained by Dr. Clinton in 1998 prior to filing the present specification, was not included in the specification as filed is irrelevant to the enablement issue in question, because the hydrophobicity analysis data was encompassed in Applicants' disclosure and recitation of the requirement for at least 50-79 contiguous amino acids of ECDIIIa in the claimed polypeptides. Again, enablement turns on whether undue experimentation would be required to practice the invention as presently claimed. The teachings of the Specification, along with the recitation of the requirement for at least 50-79 contiguous amino acids of ECDIIIa in the claimed polypeptides, and the skill in the art relating to these receptors (as described above) ensures that undue experimentation would not be requied to practice the invention as presently claimed.

Conclusion. In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, as well as all of the reasons previously made of record, Applicants respectfully submit that one of skill in the art could readily make and use the presently claimed subject matter without undue experimentation.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rebuttal to Examiner's Arguments:

Applicants point out that the Examiner's enablement analysis is highly biased toward the 'predictability' factor. Applicants respectfully submit that it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. Instead, the Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. In re Wands, at 737. Thus, Applicants respectfully submit that the Examiner's allegation that protein chemistry is unpredictable not only improperly considers only one factor, but even this factor has not been treated properly in view of the specification teachings, and the Affidavit record.

Applicants again point out and submit that the Examiner's reliance on Rochester v. Searle (358 F.3d 916, Fed Dir., 2004), which is a written description based case, is misplaced, and stands as testament to the Examiner's misunderstanding of U.S. patent law on enablement. Rochester addresses lack of satisfaction of the written description requirement, not the enablement requirement. It is well-established that the written description and enablement requirements of 35 U.S.C. § 112, first paragraph are separate and distinct. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. § 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement.) That is to say that an invention can be fully described without being enabling, and may enable one skilled in the art to make or use the claimed invention without providing adequate description. See also MPEP § 2161.

In addition, the facts pertinent to the findings in Rochester are **fundamentally** distinct from the instant claims. The claims at issue in Rochester related to U.S. Patent No. 6,048,850 ("the '850 patent") were directed toward methods for selectively inhibiting mammalian prostaglandin H

synthase-2 (PGHS-2 or COX-2) by administering a non-steroidal compound that selectively inhibits activity of a PGHS-2 gene product. Having identified the distinct functions between PGHS-1 and PGHS-2, the scientists developed an assay for identifying a non-steroidal compound that would selectively inhibit PGHS-2. While the `850 patent described the assay, it did not include **any** compounds identified by its use. Thus, the court concluded that the '850 patent lacked adequate written description; the question of enablement was considered moot and not addressed in the Federal Circuit decision.

In Rochester, all of the claims at issue were directed toward "A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product … ." Id. at 69 U.S.P.Q.2d 1888. The "patent neither disclose[d] any such compound nor provide[d] any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research." Id., 69 U.S.P.Q.2d at 1889 (citing Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp. 2d 216, 224-25, 228-29, 68 U.S.P.Q.2d 1424 (W.D.N.Y. 2003)) "[T]he [trial] court found no evidence in the '850 patent that the inventors themselves knew of any such compound at the time their patent application was filed." Id.

Further, the Federal Circuit found "[e]ven with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, let alone have been within the purview of one of ordinary skill in the art in the 1993-1995 period in which the applications that led to the '850 patent were filed" and the patent owners experts did not offer any persuasive evidence to the contrary:

By contrast, the instant claims are NOT merely directed to screening assays, but are directed to specific polypeptides, which are explicitly disclosed in the application as filed. The instant

application provides polypeptides, including both structural and functional elements, as well as a process for sequencing, cloning, purifying, and testing the polypeptides. Applicants' "genus" encompasses the exemplified species and other species that are similar because they exhibit all or part of the sequence of SEQ ID NO:1 or SEQ ID NO:2 and also bind the ECD of HER-2. Thus, Rochester is improperly cited and at best, misplaced.

The Examiner concedes that the teachings of the working examples set forth in the instant application exemplify how to clone, purify and test the binding affinity of the polypeptides and fragments, but nonetheless goes on to urge that such teachings are insufficient, since the claims are allegedly not drawn to the various working examples, but instead are "drawn to the unpredictability of protein chemistry," and thus are allegedly not enabled. (*See* p.5 second full paragraph, Office Action dated May 23, 2007.)

Applicants respectfully disagree with this characterization of the claimed subject matter. Applicants respectfully reiterate that in light of all of the Wands Factors, the instant application fully enables the scope of the instant claims.

The Examiner also alleges that while the facts of Rochester are not similar, "both cases are drawn to drugs effective for treatment, (2) both cases are drawn to specific structures that have not been identified, (3) both bases (sic) require that screening assays be used to identify the structures that would be expected to function as claimed." (*See* p. 11, bottom of first full paragraph, Office Action dated May 23, 2007.)

Applicants respectfully disagree with this characterization and submit that factors (2) and (3) indicated by the Examiner as being common with Rochester in fact are distinct in that the structures of the claimed subject matter have clearly been identified and exemplary characterizations made in the instant application, and that such was clearly not the case in Rochester. As previously made of record, the SEQ ID NOs of the claimed polypeptides are

disclosed in the application. Likewise, the region of the claimed polypeptides that is required for binding is disclosed in the instant application as at least 50-79 amino acids in length. Finally, while simple testing assays may facilitate practice of certain aspects of the instant claims, such routine testing does not rise to the level of undue experimentation according to the Wands Factors outlined above.

Importantly, the specification teaches that a polypeptide *comprising* SEQ ID NO:1 (*i.e.* a his-tagged ECDIIIa peptide, or p68HER-2) binds to p185HER-2. Given the guidance in the specification, one of skill in the art could predictably make the polypeptides as claimed, such as by using standard recombinant DNA techniques and confirm the resulting polypeptides for their ability to bind p185HER-2. Furthermore, as is apparent from the Affidavit of Dr. Gail Clinton, the recitation of "50-79 contiguous amino acid residues..." not only serves to memorialize Applicants' knowledge gained from the location of the central ECDIII a hydrophobicity region, but also serves as a scientifically-based 'road-map' for the construction of active truncated fragments.

Additional Rejection under 35 U.S.C. §112, first paragraph

Claims 18-20 and 29-30 remain rejected, under 35 U.S.C. §112, first paragraph, as allegedly being broader than the enabling disclosure. Specifically, it is alleged that while the specification is enabling for a pharmaceutical composition for treating solid tumors that overexpress HER-2, where the composition comprises a polypeptide of SEQ ID NO:2, the specification does not reasonably provide enablement for any pharmaceutical composition containing a polypeptide whose sequence consists of SEQ ID NO:1, comprises SEQ ID NO:1, or comprises the claimed fragments of SEQ ID NO:1 or SEQ ID NO:2. The Examiner concedes that "although it is clear that the polypeptides can be formulated as pharmaceutical compositions, the art recognizes the unpredictability of the cancer treatment arts contemplated in the specification and... no one of ordinary skill in the art would

believe it more likely than not that the broadly claimed invention would function as claimed." (*See* pg. 13, first full paragraph.)

Applicants respectfully traverse this rejection and submit that the claims are fully enabled by the instant application at the time of filing. Specifically, as conceded by the Examiner, "it is clear" from the teachings of the specification that the polypeptides can be formulated as pharmaceutical compositions. Additionally, as previously made of record, the specification provides explicit teaching of anti-tumor cell activity by p68HER-2 in an assay assessing anchorage independent growth of cells in soft agar, which is an art recognized and predictive procedure to examine transforming activity (see *e.g.*, page 13, lines 5-23, and Figure 7). Specifically, the specification teaches that p68HER-2 inhibits anchorage independent growth of two cells lines (SKOV-3 and 17-3-1 cells, both which overexpress HER-2). In addition, the Declarations of record of November 22, 2002 by Dr. Gail Clinton and Dr. Edward Neuwelt further demonstrate the efficacy of p68HER-2 in *in vivo* models of tumor cell activity using other art recognized assays that were known to one of skill in the art at the time of filing the instant application.

Applicants respectfully submit that the requirements for patentability are separate and distinct form those required for new drug approval from the Food and Drug Administration. Applicants respectfully submit that the Examiner provides no basis for support for the conclusory statement that "no one of ordinary skill in the art would believe it more likely than not that the broadly claimed invention would function as claimed," particularly following immediately after the concession that "it is clear" that the polypeptides can be made into pharmaceutical drugs.

Applicants respectfully note that, as stated herein, the determination of enablement is based on the evidence as a whole, and "the examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence." *See* MPEP 2164.05 (emphasis original). Applicants respectfully submit that if the Examiner is

relying on "common knowledge" or "taking official notice," with regard to the statement that "no one of ordinary skill in the art would believe it more likely than not that the broadly claimed invention would function as claimed," then the examiner must provide documentary evidence in the next Office Action if the rejection is to be maintained. *See* 37 C.F.R. §1.104(c)(2); MPEP 2144.03. Applicants further submit that if the Examiner is relying on personal knowledge to support the finding of what is known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. *See* 37 C.F.R. §1.104(d)(2).

Finally, the Declarations, and references of record therein, evidence the high level of skill and high level of knowledge in the art, particularly with respect to assaying for compounds for treating solid tumors. Thus, it is respectfully submitted that the high degree of knowledge that was available at the time of filing of the instant application, in combination with the teachings of the specification, render the instantly claimed compositions predictably generated and tested for anti-tumor activity. Furthermore, as is apparent from the attached Affidavit of Dr. Gail Clinton, the recitation of "50-79 contiguous amino acid residues..." did not only serve to memorialize the knowledge gained from the location of the central hydrophobicity region, but also serves as a scientifically-based 'road-map' for the construction of active truncated fragments.

Applicants, therefore, respectfully submit that this rejection has been overcome, and request withdrawal of this rejection.

Further Rejection under 35 U.S.C. §112, first paragraph

Claims 8-10, 18, 29, and 30 stand rejected, under 35 U.S.C. §112, first paragraph, as allegedly lacking *written description*.

Specifically, the Examiner alleges that there is no support for recitation of 'an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, or a fragment thereof wherein

the polypeptide binds to the extracellular domain of HER-2 with an affinity binding constant of at least 10^8 M^{-1}.

Applicants respectfully traverse this rejection and submit that the original specification describes a *genus* of compounds that comprises SEQ ID NO:1, or 50-79 contiguous amino acid-containing fragments thereof, and that bind at nanomolar concentrations, meaning that they would have a binding affinity "of at least 10^8" as recited. Applicants point out that SEQ ID NOS: 1 and 2 are related, in that SEQ ID NO:1 is comprised within SEQ ID NO:2. Clearly, because SEQ ID NO:2 or any polypeptide comprising SEQ ID NO:2, or that comprises the C-terminal contiguous 79 amino acid residues thereof, would also comprise SEQ ID NO:1 and would thus be encompassed by a *genus* of compounds that comprises SEQ ID NO:1, or 50-79 contiguous amino acid-containing fragments thereof, and that bind at nanomolar concentrations (i.e., affinity of at least 10^8).

Moreover, it is clear from the specification that Applicants considered that p68HER-2 bound at least as well, if not better than the ECDIIIa subportion thereof. The specification at page 7 for example, in the legend to Figure 7, describes the use of nanomolar concentrations of p68HER-2 for binding to SKOV-3 cells. Additionally, the specification at page 8, recites that "the unique ECDIIIa peptide binds with high affinity (nM concentrations) to p185HER-2 and to transfected 17-3-1 cells that overexpress p185HER-2 (Figure 5)," and further states that "[t]herefore, p68HER-2 and fragments thereof appear to be a naturally occurring HER-2 binding protein, encoded by the HER-2 gene." Therefore, the SEQ ID NO:1 containing fragments are disclosed as binding with an affinity of at least 10^8 and are referred to as high affinity binders that can be used a nanmolar concentration. The specification clearly teaches that p68HER-2 (SEQ ID NO:2) is also regarded as binding with an affinity of at least 10^8, because it is used at nanomolar concertrations in the specification Examples, and as described above, SEQ IN NO:2 or any polypeptide comprising SEQ ID NO:2, or that comprises the C-terminal contiguous 79 amino acid residues thereof, would also

comprise SEQ ID NO:1 and would thus be encompassed within, and thus defined by a *genus* of compounds that comprises SEQ ID NO:1, or 50-79 contiguous amino acid-containing fragments thereof, and that binds at nanomolar concentrations (i.e., affinity of at least 10^8).

Applicants respectfully note that the Examiner does not dispute the content of the disclosure, yet provides no basis for maintaining this rejection. Instead, the Examiner provides the mere conclusory statement that Applicants' argument has been considered, "but has not been found persuasive and the rejection is maintained." (*See* page 14, last sentence, Office Action dated May 23, 2007.) Applicants respectfully note that such conclusory statement is improper without basis for such statement. Applicants note that it is necessary to "fully respond to applicant's rebuttal arguments, and properly treat any showings submitted by applicant in the reply," when maintaining a rejection under 35 U.S.C. § 112, first paragraph. *See* MPEP 2163.04.

Claims 8-10 and 18 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking *written description*.

Specifically, the Examiner alleges that claims 8-10 and 18 lack proper written description because they are drawn to polypeptides comprising "at least one N-linked glycosylation site." The Examiner alleges that there is no support in the specification for the limitation of "at least one N-linked glycosylation site." Additionally, the Examiner has also called out claim 9 for including the limitation of "at least three N-linked glycosylation sites."

Applicants respectfully traverse this rejection and submit that there is explicit literal support for glycosylation sites throughout the instant application, for example at page 5, line 23, and page 16 line 5, where the specification describes "a consensus asparagine linked glycosylation site." As recognized in the art, and including to one of ordinary skill in the art, "N-linked" and "asparagine linked" refer to the same amino acid, since "N" is the single letter abbreviation for asparagine. The

specification thus teaches a single asparagine linked site at page 5, line 23, and page 16 line 5, and there is consequently support in the specification for the limitation of "at least one N-linked glycosylation site" recited in claims 8-10 and 18.

Furthermore, the specification discloses that subdomains I and II of the ECD portion of herstatin contain five N-glycosylation sites and that the novel 79 amino acid portion contains one consensus N-linked glycosylation site. Thus, a polypeptide of 80-419 amino acids that contains the 79 amino acid portion has "at least one" N-linked glycosylation site present, and depending on the length of the polypeptide, other N-linked glycosylation sites may also be present. Thus, Applicants respectfully request that this rejection be withdrawn as it applies to claims 8-10 and 18.

Applicants respectfully note that the Examiner concedes that there is explicit support for "at least three N-linked glycosylation sites," at page 3, lines 14-21 of the instant specification. (*See* page 16, first full paragraph.) Thus, Applicants respectfully request that the rejection as it applies to claim 9 be withdrawn in light of the concession of support in the instant application for "at least three N-linked glycosylation sites."

Applicants, therefore, respectfully request withdrawal of the Examiner's new matter rejection based on an alleged lack of written description for the number of glycosylation sites, where there is explicit literal support in the originally filed specification as cited herein, and as appreciated by the Examiner.

Claims 18 and 30 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking *written description*.

Specifically, the Examiner alleges that there is no support for recitation of "combinations thereof, with the proviso that where the composition comprises the monoclonal antibody it also comprises at least one of the agents of (a) and (b)."

Applicants respectfully traverse this rejection, based on the fact that there is explicit literal support for this limitation on page 9, line 31 through page 10 line 9, where the specification describes:

"The present invention further provides a pharmaceutical composition for treating solid tumors that overexpress HER-2, comprising an agent selected from the group consisting of (a) an isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1, wherein the polypeptide binds to the extracellular domain ECD of HER-2 at an affinity of at least 10^8, (b) an isolated and glycosylated polypeptide having from about 300 to 419 amino acids taken from the sequence of SEQ ID NO. 2, wherein the C terminal 79 amino acids are present, and wherein at least three N-linked glycosylation sites are present, (c) a monoclonal antibody that binds to the ECD of HER-2, and (d) **combinations thereof**, with the proviso that the agent cannot be the monoclonal antibody alone, and pharmaceutically acceptable carrier. Preferably, the agent is the isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1. Most preferably, the agent is a combination of the isolated polypeptide having from about 50 to 79 amino acids taken from the sequence of SEQ ID NO. 1 and the monoclonal antibody that binds to the ECD of HER-2."

Specification page 9, line 31 through page 10 line 9 (emphasis added).

Applicants' explicit recitation of "combinations thereof", by virtue of reciting "thereof", does not allow the proviso ("that the agent cannot be the monoclonal antibody alone") to be interpreted as allowing the antibody to be in combination with "any second agent" (in the absence of (a) or (b)). Applicants respectfully submit that according to basic principles of claim interpretation, "combination thereof" must necessarily be combinations contained in the grouping (i.e., of (a) (b) and (c)), and cannot be combinations of (c) with "any second agent" that is not (a) or

(b). Furthermore, the combined phrases "combinations thereof" and "that the agent cannot be the monoclonal antibody alone" necessitates that the antibody must be present with at least one of agents (a) and (b).

Applicants respectfully submit that claim 18 recites "that where the composition comprises the monoclonal antibody it also comprises at least one of the agents of (a) and (b)," and is this fully supported by the originally filed specification. Applicants further respectfully submit that it is not necessary that the claimed composition is not limited to a monoclonal antibody and only (a) and (b) as additional agents.

Applicants, therefore, respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request entry of the present Response and Amendment, and earnestly solicit a Notice of Allowance relating to all pending claims, all having been previously allowed.

The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite issuance of a final Notice of Allowance.

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Respectfully submitted,
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